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Original Article

# Group and Individual Change in Cognitive Functioning in Patients With 1 to 10 Brain Metastases Following Gamma Knife Radiosurgery

W.C.M. Schimmel [*†‡1], E. Verhaak [*†‡1], M. Bakker [§], P.E.J. Hanssens [*†], M.M. Sitskoorn [†‡], K. Gehring [*†‡]

[*] Gamma Knife Center, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands
[†] Department of Neurosurgery, Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands
[‡] Department of Cognitive Neuropsychology, Tilburg University, Tilburg, the Netherlands
[§] Department of Methodology and Statistics, Tilburg University, Tilburg, the Netherlands

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## Abstract

*Aims:* Stereotactic radiosurgery is increasingly used to treat multiple (four or more) brain metastases. Preserving cognitive functions is a highly relevant treatment goal because cognitive deteriorations may negatively affect a patient's quality of life. The aim of this study was to assess cognitive change, at the group and individual level, in patients with 1 to 10 brain metastases up to 9 months after Gamma Knife radiosurgery (GKRS).

*Materials and methods:* Ninety-two patients with 1 to 10 newly diagnosed brain metastases, expected survival >3 months and Karnofsky Performance Status (KPS) ≥70 and 104 non-cancer controls were included. A neuropsychological test battery was administered before GKRS ($n = 92$) and at 3 ($n = 66$), 6 ($n = 52$) and 9 ($n = 41$) months after GKRS. The course of test performances, while taking into account practice effects, was analysed using linear mixed models. Pre-GKRS predictors of cognitive trajectories were analysed. To determine proportions of individuals with cognitive changes, reliable change indices, with correction for practice effects, were calculated.

*Results:* At the group level, immediate memory, working memory and information processing speed significantly improved over 9 months after GKRS. There were no cognitive declines. Neither number nor volume of brain metastases influenced cognitive change over time. At the individual level, proportions of patients with stable, improved or declined performances were comparable with controls, except for information processing speed (more individuals with improvements in patients) and motor dexterity (more improvements and declines in patients).

*Conclusions:* Cognitive functioning in patients with 1 to 10 brain metastases was preserved, or improved, up to 9 months after GKRS. Neither number nor volume of brain metastases influenced cognitive performance.



*Key words:* Brain metastases; cognitive functioning; Gamma Knife radiosurgery; individual changes; stereotactic radiosurgery

## Introduction

Life expectancy in patients with brain metastases is increasing due to improvements in systemic treatments of the primary tumour [1,2]. Already before brain metastases treatment, patients may suffer from cognitive impairments caused by an interplay of factors, including the brain metastases themselves, the primary tumour and its treatments, and the patient's functional status [3,4]. These impairments often concern slow processing of information and memory problems and may negatively affect daily functioning and quality of life [3].

A review on the cognitive effects after stereotactic radiosurgery (SRS) concluded that patients with brain metastases experience little to no objective cognitive decline in the early phase after SRS, followed by a trend towards improvement or stabilisation up to 12 months after SRS [5]. Furthermore, evaluation of individual cognitive changes after SRS showed that in most patients with brain metastases, cognitive functions remained stable for at least 6 or 12 months after SRS [6,7].

Author for correspondence: W.C.M. Schimmel, Prof. Cobbenhagenlaan 225, Simon Building, Room S221, 5037 DB, Tilburg, the Netherlands. Tel: +31-13-466-3118.

*E-mail address:* w.c.m.schimmel@tilburguniversity.edu (W.C.M. Schimmel).

[1] Co-first authors.

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In recent years, the total volume of brain metastases has become a more prominent eligibility criterion for SRS as opposed to the absolute number of brain metastases [8]. Although the application of SRS is rapidly expanding to patients with multiple (more than four) brain metastases, previous studies on cognitive outcomes after SRS mostly included patients with a limited number of brain metastases (one to four). These studies found no association, based on univariate analyses and uncorrected for multiple testing, between the number of brain metastases and cognitive test performance, whereas higher total brain metastases volume was significantly associated with worse attention, information processing and executive functions [4,9].

Cognitive outcomes after SRS in patients with more than four brain metastases, as measured with an objective neuropsychological test battery, have not been evaluated thus far. Only one recent study, which used the Hopkins Verbal Learning Test as a single neuropsychological test, reported on stable memory performance up to 12 months after SRS in most patients with multiple (>10) brain metastases [7].

Furthermore, none of the previous studies corrected for potential practice effects (i.e. improvements in performances due to familiarity with test items and test procedures [10,11]). Practice effects should be taken into account to avoid a potential underestimation of cognitive decline, even when using parallel/alternative versions of the same test [10,11].

The aim of this study was to evaluate group and individual cognitive change, while taking into account practice effects, in patients with 1 to 10 brain metastases up to 9 months after Gamma Knife radiosurgery (GKRS). If cognitive functioning could be preserved at the pre-treatment level, this would suggest that GKRS does not cause additional cognitive decline. In addition, potential predictors of cognitive performance over time were analysed.

## Materials and Methods

Cognition and Radiation-Study A (CAR-Study A; NCT02953756) is a prospective observational study and was approved by the Medical Ethics Committee Brabant (NL53472.028.15). We previously described baseline cognitive performances and health-related quality of life (HRQoL), and the course of fatigue in this patient group [12–14].

### *Patients and Procedures*

Patients with 1 to 10 newly diagnosed brain metastases (total volume ≤30 $cm^3$), Karnofsky Performance Status (KPS) ≥70 and expected survival >3 months were recruited. Additional eligibility criteria and procedures have previously been described [12,14].

A baseline neuropsychological assessment (NPA), including neuropsychological tests and questionnaires on anxiety and depression, fatigue and HRQoL, was carried out in the morning before GKRS. Follow-up assessments, combined with clinical follow-ups, were carried out 3, 6 and 9 months after GKRS. All patients gave written informed consent before the first NPA.

### *Non-cancer Controls and Procedures*

For normative purposes, non-cancer controls [13,14] were recruited from the general community and the broad network of the research group. Controls were selected to be, as much as possible, comparable with the general population and our patient group (frequency matching). Exclusion criteria included a (history of) cancer diagnosis or severe cerebrovascular disease in the past 12 months. Follow-up assessments were carried out at 3 and 6 months after the first NPA.

### *Treatment*

GKRS was carried out with a Leksell Gamma Knife® ICON™ (Elekta Instruments AB, Stockholm, Sweden). All patients received a dose of 18–25 Gy with 99–100% coverage of the target. Given the high conformity and selectivity of GKRS, organs at risk (brainstem, optic nerves and chiasm) were only segmented and optimised in the GKRS planning workflow when relevant. Dose limits for these organs were 18 Gy for the brainstem and 8 Gy for the optic nerves and chiasm. No attempt was made to delineate the hippocampus nor was there a dose limit set for the hippocampus.

### *Measures*

Sociodemographic and clinical characteristics were retrieved from patients' medical health records. Cognitive functioning was measured with a well-established battery, including six neuropsychological tests: Hopkins Verbal Learning Test-Revised with six parallel versions (immediate and delayed verbal memory and recognition), Trail Making Test (TMT-A; psychomotor speed and TMT-B; cognitive flexibility), Controlled Oral Word Association with two parallel versions (COWA; word fluency), Wechsler Adult Intelligence Scale (WAIS) Digit Span (attention span and working memory), WAIS Digit Symbol (information processing speed) and Grooved Pegboard (dominant and non-dominant hand dexterity) [3,15].

The total volumetric sum of contrast-enhancing brain metastases was determined at baseline and at 3, 6 and 9 months after GKRS, using T1-weighted, contrast-enhanced magnetic resonance imaging (MRI) scans (1.5 mm slice thickness). A complete response was defined as a disappearance of all brain metastases (no longer visible). A partial response was defined as a ≥65% decrease in total tumour volume and no new brain metastases. Intracranial progression was defined as a ≥73% increase in total tumour volume or new brain metastases. Stable disease was defined as no complete response, no partial response and no intracranial progression [16].

*Statistical Analyses*

Statistical analyses were carried out with SPSS version 25, except for the linear mixed models (LMMs), which were performed with R, version 3.6.1 [17].

Independent samples *t*-tests and chi-squared tests were carried out to compare characteristics of patients with and without at least one follow-up NPA. Kaplan–Meier curves were used to analyse overall survival. Cognitive changes were determined between baseline (pre-GKRS) and 9 months (T0–T9), and for three separate time intervals: baseline and 3 months (T0–T3), 3 and 6 months (T3–T6), and 6 and 9 months (T6–T9).

Raw cognitive test scores were converted into socio-demographically adjusted *z* scores based on data from our control group (including age, sex and education as covariates): *z* score $= Y_o - Y_p/SD_{residual}$. $Y_o$ is the individual's raw test score, $Y_p$ is the predicted raw test score using regression-based formulae and $SD_{residual}$ is the standard deviation of the control group's residual [18]. For the TMT, the raw test score on TMT-A was entered as a fourth predictor variable to calculate the *z* score on TMT-B (the interference index TMT-B|A).

To correct for practice effects for the 3-, 6- and 9-month follow-up data, patients' post-GKRS *z* scores were calculated using the controls' test scores at 3 months, as the strongest practice effects occur within this time interval [10,19]. Except for the COWA, as each of the two parallel versions has a different set of letters, we used the controls' performance at 6 months to calculate post-GKRS *z* scores for patients at 6 months (a comparison with the same set of letters). An impaired test performance was defined as a *z* score $\leq -1.50$ [20]. One-sample *z*-tests were used to compare mean cognitive function of patients with controls at baseline and at 9 months. Chi-squared tests were carried out to compare the percentages of impaired test performance of patients with controls at each time point. Independent samples *t*-tests were used to compare cognitive test performances between patients with and without intracranial progression for each time point separately.

We used the *nlme* package [21] in R [17] to run 11 LMMs of the relationship between performance on each cognitive test and time. To estimate model parameters, the restricted maximum likelihood estimate (REML) method was used. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were used to estimate model fit. As random effects, the intercepts for the effect of cognition were used. Random slopes were added for psychomotor speed only. The first-order autoregressive covariance structure (AR1) at level 1 and a scaled identity matrix at level 2 was used. Time was included as a categorical variable in subsequent models to examine changes in cognitive functioning for the separate time intervals.

These LMMs were also used to examine the interaction effects between time and possible baseline predictors of cognition. The following predictors, based on results from previous studies [4,14], were analysed: KPS (low 70–80 versus high 90–100), systemic treatment before or at time of GKRS (yes versus no), total volume of brain metastases (small $<4.8$ cm$^3$, medium 4.8–12.6 cm$^3$, large $>12.6$ cm$^3$) and number of brain metastases (one to three versus four to 10).

Reliable change indices (RCIs), reflecting change at the individual level in the context of observed changes in the control group, correcting for measurement errors (including practice effects) were calculated according to formula 10 by Maassen *et al.* [22]. A change in test score from baseline to follow-up was considered reliable if it fell outside of the 90% confidence interval, corresponding to RCI values above $+1.645$ (improved performance) or below $-1.645$ (declined performance). RCI values that did not exceed these values were defined as 'stable' (no significant change). At the test level, numbers of patients with improved, stable or declined cognitive performance were then counted for each test at each time interval.

Patients were categorised, based on the RCIs, into four categories: (i) 'decline' ($\geq$2 declines and $\leq$1 improvement on any of the 11 test variables); (ii) 'improvement' ($\geq$2 improvements and $\leq$1 decline); (iii) 'both' ($\geq$2 declines and $\geq$2 improvements); (iv) 'stable' ($\leq$1 declines and $\leq$1 improvements). Chi-squared or Fisher exact tests were conducted to compare the proportions of participants in each category between patients and controls. For T0–T9 and T6–T9, the proportions of patients were compared with the proportions of controls between T0–T6 and T3–T6, respectively.

To control for the false discovery rate due to multiple testing, a corrected alpha, based on the procedure of Benjamini and Hochberg [23], was used per hypothesis.

## Results

*Characteristics and Compliance*

In total, 92 patients and 104 controls were included (Table 1). Patients and controls did not differ in sex, age and education. Forty per cent of patients had four to 10 brain metastases. The 1-year survival rate was 48.9% and the median overall survival was 11.8 months. The cognitive tests were completed by 66 of 76 (86.8%), 52 of 68 (76.5%) and 41 of 57 (71.9%) patients alive at 3, 6 and 9 months, respectively. Reasons for dropout, apart from death ($n = 24$), were: NPA was considered too burdensome ($n = 13$), no follow-up MRI scan as it was not clinically meaningful due to poor neurological/physical condition ($n = 12$) and follow-up elsewhere ($n = 2$). Of the 66 patients with at least one follow-up, 34 patients (51.5%) had intracranial progression (in 18 patients due to new lesions only; 52.9%), 15 patients (22.7%) had a partial or a complete response and 17 patients (25.8%) had stable disease between time of treatment and last follow-up. Clinical characteristics did not significantly

differ between patients with or without follow-up. Patients without ($n = 26$) versus patients with at least one follow-up NPA ($n = 66$) had shorter survival (2.7 versus 17.1 months, $p < .001$).

*Cognitive Status at Baseline and at 9 Months – Group and Individual Level*

At baseline, patients performed significantly worse on all tests compared with controls ($p < .05$; range mean z scores: −0.21 to −1.63; supplementary Table S1 summarises the mean z scores). The lowest mean scores were found for non-dominant hand dexterity, cognitive flexibility and information processing speed. At 9 months after GKRS, patients performed significantly worse than controls on seven of 11 tests ($p < .03$; range mean z scores: −0.49 to −1.40). The lowest performances were found for dominant and non-dominant hand dexterity, information processing speed and psychomotor speed. Mean cognitive test performances were comparable for patients with or without intracranial progression at 3 ($n = 14$ versus $n = 52$), 6 ($n = 17$ versus $n = 35$) and 9 months ($n = 17$ versus $n = 24$) after GKRS (data not shown). At the individual level, significantly more patients had impaired performances than controls: at baseline for nine (15.2–55.3%) of 11 tests ($p \leq .04$) and at 9 months for seven (22.0–32.4%) of 11 tests ($p < .03$; supplementary Table S2 summarises the percentages of impaired performances for patients and controls).

*Change in Cognitive Performance – Group Level*

Over 9 months, cognitive performance remained stable, except for significant improvements in immediate memory, working memory and information processing speed. More specifically, working memory improved significantly between baseline and 3 months, and information processing speed improved significantly between 3 and 6 months. Although verbal recognition and verbal fluency did not change over 9 months, verbal recognition improved significantly between 3 and 6 months and decreased significantly between 6 and 9 months; the reverse was observed for verbal fluency (first decrease, and then improvement) (Table 2).

*Predictors of Cognitive Performance over Time – Group Level*

Patients with low (versus high) KPS had significantly more improvement over time in verbal recognition. No other significant predictors were found. Neither number nor volume of brain metastases influenced cognitive performance over time (supplementary Table S3 shows the linear mixed model results for the baseline predictors of cognitive performances over time).

*Individual Change in Cognitive Performance – Test Level*

Although the proportions of patients with declined, stable or improved performance at the test level fluctuated across the time intervals, there were no significant differences in proportions between patients and controls, except for information processing speed, and dominant and non-dominant hand dexterity (see Figure 1 and supplementary Tables S4 and S5, which summarise the individual cognitive changes in patients and controls, respectively). For information processing speed, over 9 months, and especially in the first 3 months post-GKRS, significantly more patients (versus controls) had improved performance (24.3% and 11.7%), and significantly fewer patients had stable scores (70.3% and 81.7%). For dominant hand dexterity, significantly more patients had declined (16.4%) or improved (18.0%) performance in the first 3 months only. For non-dominant hand dexterity, significantly more patients had declined (24.4%) or improved (26.8%) performance over 9 months.

*Individual Change in Cognitive Performance – Patient Level*

Over 9 months, test performance remained stable in 39.4% of patients and improved in 33.3% of patients; 21.2% of patients showed a decline and 6.1% of patients had both improvements and declines (Figure 2). Compared with controls, significantly fewer patients had stable performance (39.4% versus 77.0%) and more patients showed an improvement in test performance (33.3% versus 13.1%).

Regarding the separate time intervals, 63.5–73.3% of the patients had stable test performances and 15.4–23.5% of patients had declined test performances. Improved performances were found in 11.1–21.2% of patients (no patients were categorised as 'both'; Figure 2). There were no significant differences in the proportions of patients and controls with declined, stable or improved test performances ($p$-values $> .14$; data not shown).

## Discussion

In this study, we evaluated group and individual level cognitive performance, corrected for practice effects, up to 9 months after GKRS in patients with up to 10 brain metastases. Already at baseline, mean performances were worse in patients on all cognitive tests compared with controls, and at the individual level, percentages of impairment were significantly higher for most tests.

Over 9 months after GKRS, patients' performances improved for immediate verbal memory, working memory and information processing speed. Performances on all other measures remained stable. Previous studies showed little to no objective cognitive decline after SRS in patients with one up to four brain metastases [4,9,24]. Compared with our study, these studies had a shorter follow-up and/or smaller patient samples at follow-up. None of the previous studies on cognitive functioning of patients with brain metastases after SRS took practice effects into account [5], which could have led to a potential underestimation of cognitive decline [10,11]. In our study, with correction for practice effects, still no decline in group performances over 9 months were found in patients with 1 to 10 brain metastases. However, analyses of the separate time intervals

**Table 1**
Characteristics

| | Patients included at baseline | Controls included at baseline | Patients with ≥1 follow-up NPA | Patients without follow-up NPA |
|---|---|---|---|---|
| Participants included, *n* (%) | 92 (100%) | 104 (100%) | 66 (72%) | 26 (28%) |
| Sex, male, *n* (%) | 47 (51%) | 50 (48%) | 31 (47%) | 16 (62%) |
| Age in years, mean ± SD (range) | 62 ± 10 (31–80) | 60 ± 10 (31–87) | 62 ± 9 (31–80) | 61 ± 11 (39–76) |
| Educational level, *n* (%)* | | | | |
| Low | 28 (30%) | 25 (24%) | 16 (24%) | 12 (46%) |
| Middle | 37 (40%) | 33 (32%) | 30 (46%) | 7 (27%) |
| High | 27 (29%) | 46 (44%) | 20 (30%) | 7 (27%) |
| KPS, *n* (%) | | | | |
| 70–80 | 33 (36%) | NA | 21 (32%) | 12 (46%) |
| 90–100 | 59 (64%) | | 45 (68%) | 14 (54%) |
| GPA | | | | |
| Class 2 | 15 (16%) | NA | 13 (20%) | 2 (8%) |
| Class 3 | 60 (65%) | | 41 (62%) | 19 (73%) |
| Class 4 | 17 (19%) | | 12 (18%) | 5 (19%) |
| Number of brain metastases, *n* (%) | | | | |
| 1–3 | 55 (60%) | NA | 42 (64%) | 13 (50%) |
| 4–10 | 37 (40%) | | 24 (36%) | 13 (50%) |
| Total volume of brain metastases, median (range)†,‡ | 5.6 (0.02–31.1) | NA | 5.9 (0.02–31.1) | 5.3 (0.04–31.0) |
| Small (<4.8 $cm^3$) | 40 (44%) | | 28 (42%) | 12 (46%) |
| Middle (4.8–12.6 $cm^3$) | 25 (27%) | | 17 (26%) | 8 (31%) |
| Large (>12.6 $cm^3$) | 27 (29%) | | 21 (32%) | 6 (23%) |
| Primary tumour, *n* (%) | | | | |
| Lung | 55 (60%) | NA | 40 (61%) | 15 (58%) |
| Renal | 15 (16%) | | 11 (17%) | 4 (15%) |
| Melanoma | 12 (13%) | | 7 (11%) | 5 (19%) |
| Other | 10 (11%) | | 8 (12%) | 2 (8%) |
| Systemic therapy§ | | | | |
| No | 39 (42%) | NA | 28 (42%) | 11 (42%) |
| Yes | 53 (58%) | | 38 (58%) | 15 (58%) |
| Chemotherapy‖ | 37 (40%) | | 28 (42%) | 9 (35%) |
| Median overall survival (months) (95% confidence interval) | 11.8 (8.6–15.0)¶ | NA | 17.1 (10.6–23.7)** | 2.7 (1.7–3.7)†† |

GPA, graded prognostic assessment; KPS, Karnofsky Performance Status; NA, not applicable; NPA, neuropsychological assessment; SD, standard deviation.

* Educational level (Verhage [31]; seven levels): low = 1–4; middle = 5; high = 6–7.

† By patient (one patient had a total tumour volume 31.1 $cm^3$ on the planning magnetic resonance imaging scan).

‡ Nineteen of 92 (21%) patients had a total volume of brain metastases >15 $cm^3$.

§ Before or at time of Gamma Knife radiosurgery.

‖ Alone only or in combination with other systemic therapies.

¶ Twenty-seven patients censored (29.3%).

** Twenty-five patients censored (37.9%).

†† Two patients censored (7.7%).

Percentages may not add up to 100% due to rounding.

showed both cognitive improvements and declines. This indicates that although the overall course remained stable up to 9 months after GKRS, fluctuations in test performances at the group level do occur within the intervals.

Baseline KPS influenced change in test performance for only one of 11 tests (more improvement over time in verbal recognition in patients with lower baseline KPS). In line with previous studies [4], the number of brain metastases did not influence cognitive change over time in multivariate analyses. Neither did we find a statistically significant association between brain metastases volume and change in cognitive performance. This is in contrast with previous studies based on univariate analyses that found significant negative associations between total brain metastases volume and attention, information processing and executive functions [4,9].

In accordance with the results at group level, and with van der Meer *et al.* [6], for most patients, both at the patient level and at the test level, cognitive functioning remained stable or improved over 9 months after GKRS, except for non-dominant hand dexterity. Performance on non-dominant hand dexterity, a measure that was not included in the study of van der Meer *et al.* [6], varied considerably at the individual level: there were significantly

**Table 2**
Course of cognitive functioning in patients with brain metastases after radiosurgery

| | Time slope T0–T9 | | | Interval T0–T3 | Interval T3–T6 | Interval T6–T9 |
|---|---|---|---|---|---|---|
| | Beta (SE) | F-value | *P** | Beta (SE) | Beta (SE) | Beta (SE) |
| Immediate verbal memory | 0.16 (0.1) | 7.282 | **.008** | 0.28 (0.1) | 0.09 (0.1) | 0.08 (0.2) |
| Delayed verbal memory | −0.01 (0.0) | 0.022 | .883 | 0.09 (0.1) | −0.04 (0.1) | −0.09 (0.2) |
| Verbal recognition | 0.09 (0.1) | 3.224 | .075 | 0.13 (0.1) | **0.52 (0.2)** | **−0.62 (0.2)** |
| Psychomotor speed | −0.04 (0.1) | 0.202 | .654 | −0.38 (0.2) | 0.14 (0.2) | 0.17 (0.2) |
| Cognitive flexibility | 0.23 (0.1) | 3.358 | .069 | 0.57 (0.3) | 0.25 (0.3) | −0.27 (0.3) |
| Verbal fluency | −0.08 (0.0) | 3.479 | .064 | −0.12 (0.1) | **−0.32 (0.1)** | **0.33 (0.1)** |
| Attention span | −0.04 (0.0) | 1.590 | .209 | −0.14 (0.1) | 0.09 (0.1) | −0.11 (0.1) |
| Working memory | 0.22 (0.1) | 19.295 | **<.001** | **0.52 (0.1)** | 0.08 (0.1) | 0.03 (0.2) |
| Information processing speed | 0.17 (0.0) | 15.333 | **<.001** | 0.12 (0.1) | **0.33 (0.1)** | 0.00 (0.1) |
| Dominant hand dexterity | 0.06 (0.1) | 0.277 | .600 | 0.27 (0.2) | 0.20 (0.3) | −0.42 (0.3) |
| Non-dominant hand dexterity | 0.04 (0.1) | 0.230 | .633 | 0.13 (0.2) | 0.24 (0.2) | −0.38 (0.3) |

* Corrected alphas, using the Benjamini and Hochberg [23] procedure, were 0.014 for the overall models (time slope T0–T9), 0.033 for the time intervals of verbal recognition and verbal fluency, and 0.017 for the time intervals of the other cognitive tests. Bold type indicates statistical significance. T0 = baseline, T3, T6, T9 = 3, 6, 9 months.

more improvements as well as more declines in patients as compared with controls. The individual variations in motor dexterity were not reflected in our group-level results. This underlines the importance of individual-level analyses in addition to group-level analyses as the latter can mask individual cognitive changes. Regarding the separate time intervals, no significant differences were found between patients and controls in proportions of change except for information processing speed (more improvement in patients) and dominant hand dexterity (more improvement and decline in patients) during the first 3 months after GKRS.

At 9 months, performances on most tests, except for the memory tasks (including working memory), were still significantly below the normative mean of non-cancer controls. The lowest performances were found for psychomotor speed, information processing speed, and dominant and non-dominant hand dexterity. Also, frequencies of impairment were significantly higher in patients than in controls for most tests. These frequencies were highest for cognitive flexibility, information processing speed and dominant hand dexterity. This illustrates the persistent character of cognitive impairments that were already present before brain metastases treatment. The impairments in dominant hand dexterity may have negatively influenced performance on the other cognitive tasks (such as the TMT and Digit Symbol) with high motor demands [25] and may partially explain the impaired performance on psychomotor speed, cognitive flexibility and information processing. In addition, chemotherapy and certain targeted therapies can cause peripheral neuropathy in some patients [26], which may

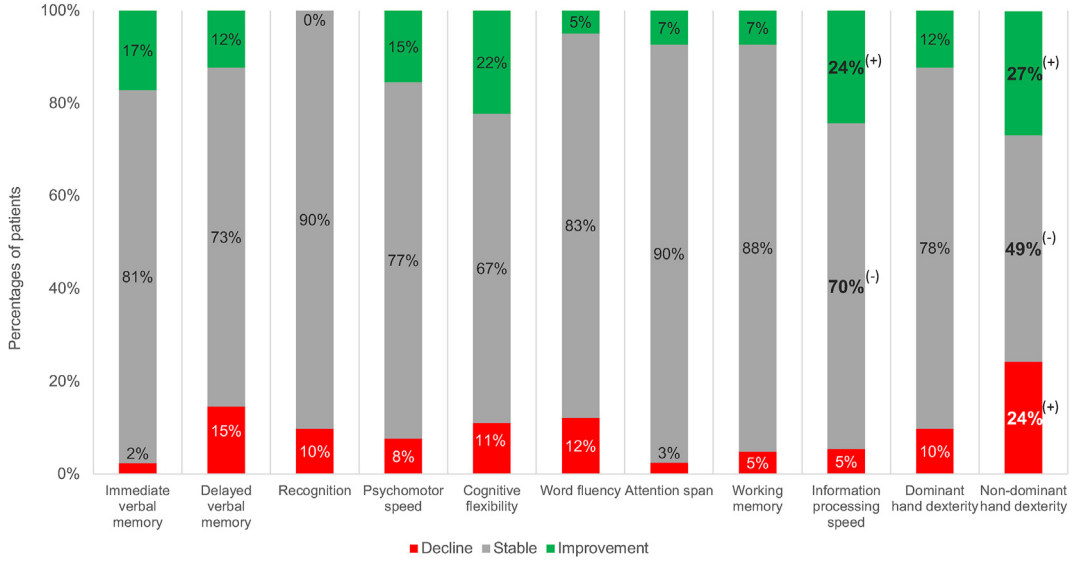


**Fig 1.** Individual cognitive changes at the test level over 9 months after radiosurgery (T0–T9; $n = 36–41$). Note: bold text indicates a statistically significant difference in the proportions of patients and controls with declined, stable or improved performance (+/− indicates that the percentage is significantly higher/lower in patients compared with controls).

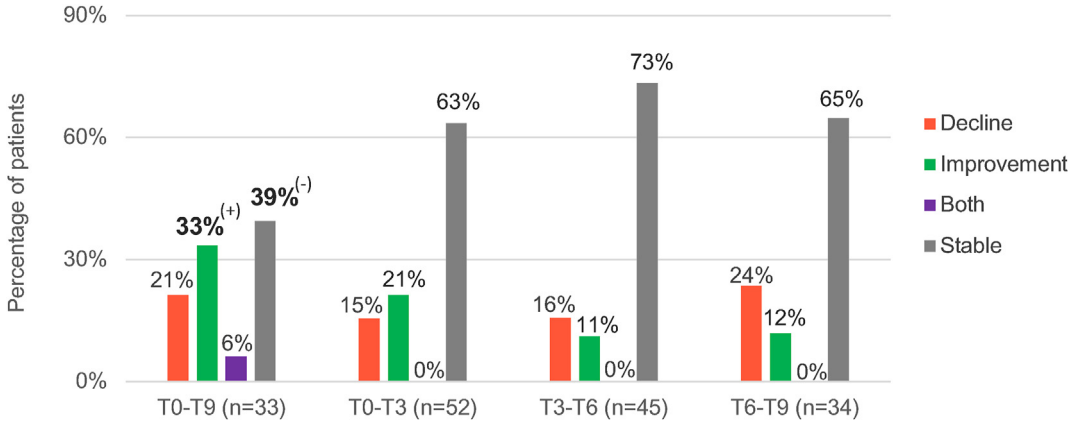


**Fig 2.** Reliable cognitive changes after radiosurgery at the individual patient level. Note: patient-level categories: (i) 'decline' (≥2 decline and ≤1 improvements on any of the 11 test variables); (ii) 'improvement' (≥2 improvement and ≤1 declines); (iii) 'both' (≥2 decline and ≥2 improvement); (iv) 'stable' (≤1 declines and ≤1 improvements). Bold text indicates a statistically significant difference in the proportions of patients and controls with declined, stable or improved performance (+/− indicates that the percentages were significantly higher (+) or lower (−) in patients compared with controls).

also partially explain the impaired performance on these tasks with motor output.

Cognitive impairments may seriously worsen the ability to carry out everyday life activities and impair patients' quality of life. Patients may encounter difficulties with processing (new) information, switching between tasks, remembering new information, performing adequate movements appropriate to a certain task, and with the ability to reason through medical treatment decisions [27]. Additionally, patients may experience time pressure, and over-stimulation, which makes it harder to engage in, and enjoy, social interactions with others. These difficulties may also increase the caregiver burden [28]. Cognitive interventions, such as rehabilitation programmes [29], may improve the quality of life/survival in these patients, especially for subgroups of patients with brain metastases who have a longer life expectancy.

This study has limitations to consider. We included a heterogeneous study sample of patients with brain metastases originating from different primary cancers. The study sample as a whole is, however, representative for the group of patients with brain metastases that is generally treated with GKRS. Patients who were willing and able to participate in this study may have been more resilient compared with non-participating patients and consequently may have performed better than non-participating patients. Moreover, although mean differences in baseline test performances and clinical characteristics between patients with and those without follow-up assessments were not statistically significant, it is likely that patients who completed the assessment at 9 months were the 'better performing' patients in terms of functional status and cognitive functioning. Additionally, the NPA was administered in the morning before treatment and at clinical follow-ups (including MRI scan and consult), during which patients may have experienced anxiety or depression. However, although patients had elevated levels of anxiety and depression, we found no evidence for a direct effect of anxiety and depression on cognitive test performance at baseline [14]. This is in line with a study by Gerstenecker *et al.* [30] in patients with brain metastases and suggests that both anxiety and depression may not be primary contributors for cognitive impairment in these patients [14,30]. Furthermore, despite the correction for practice effects and the use of parallel versions, an additional practice effect may have occurred at 9 months because these patients may have been even more familiarised with the tests and the test procedures compared with the assessments at 3 or 6 months.

To conclude, up to 9 months after initial GKRS, both at the group and individual level, most patients with 1 to 10 brain metastases showed preserved or improved cognitive functioning. This suggests that GKRS does not cause additional cognitive damage. Neither number nor volume of brain metastases influenced cognitive performance.

## Conflicts of Interest

The authors declare no (financial) conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2021.01.003.

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